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REMARKS

Reconsideration and withdrawal of the rejections of the application are requested in view of the amendments and remarks presented herein, which place the application into condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 1, 11-14, 16, 21-28 and 30 are pending in this application. Claims 1, 11-14, 16, 21, 23, 26-28 and 30 are amended. Claims 2-10, 17-20 and 29 are cancelled. Support for the amended claims can be found throughout the specification. Particular support for reduced nigrostriatal degeneration can be found in the figures, for example, in Figures 3 and 6. No new matter is added.

It should be noted that, as filed, there was no claim numbered 15 and there were two claims numbered 20. Both claims numbered 20 are cancelled by this amendment; the claims have not been renumbered to include a claim 15.

It is submitted that these claims are and were in full compliance with the requirements of 35 U.S.C. §112. The amendments of the claims herein are not made for the purpose of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112; but rather, the amendments are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendments should not give rise to any estoppel, as the herewith amendments are not narrowing amendments.

Oath or Declaration

The Examiner is thanked for pointing out the typographical error in the filed Declaration. A corrected Declaration has been prepared and will be filed upon receipt, by the undersigned, of the executed document.

Drawings

Enclosed is a Petition to Accept Color Drawings, along with copies of the color drawings, addressing item 1 of the Notice of Draftsperson's Patent Drawing Review ("the Notice"). To address item 12 of the Notice, a corrected version of Figure 4, with larger numbers, is enclosed. Also enclosed is a copy of Chief Draftsperson Gray's facsimile, waiving the requirement under item 6 of the Notice. Acceptance of the drawings is requested.

II. THE REJECTIONS UNDER 35 U.S.C. §112, 1ST PARAGRAPH, ARE OVERCOME

Claims 17 and 18 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The rejection is traversed.

Several mammalian GDNF molecules are known, and one of skill in the art would recognize that these molecules are analogous to human GDNF. Therefore, Applicants maintain that, between the teachings of the specification and the common knowledge of the skilled artisan at the time the application was filed, there is adequate description for a genus of GDNF molecules. However, in an effort to expedite prosecution, the claims have been limited to human GDNF, obviating the rejection.

Claims 1-30 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. The rejection is traversed.

Initially, and without acquiescing to any rejection of the record, Applicants would like to point out amendments, to the claims, which are made for business considerations and commercially contemplated embodiments of the invention. For example, claim 1 has been amended such that it is directed to treating Parkinson's disease by targeting a brain cell with a vector that will express GDNF, thereby reducing nigrostriatal degeneration and treating the Parkinson's. Applicants reserve the right to re-present, in continuing applications, the difference, if any, in scope of a claim resulting from an amendment to the claims herein.

With respect to the Examiner's view of the invention, Applicants take this opportunity to provide clarifying remarks with respect to the application of the Wands Factors to the currently claimed invention. Firstly, on pages 4-5 of the OA, the Examiner sets forth assertions based upon the unpredictability of the gene therapy state of the art, citing references which generally support difficulties in various parameters of gene therapy, for instance, targeting and expression, and extrapolation from animal models to humans.

Page 7 of the Office Action acknowledges that the specification provides data using primate models of Parkinson's disease; however, it asserts that there is no disclosure of an art-recognized correlation between the results obtained and the results the skilled artisan would expect to obtain in treatment of humans with Parkinson's disease. Applicants disagree, and would like to point out that the non-human primate models of the specification are in fact art-recognized models that the skilled artisan uses to make a predictable correlation to Parkinson's disease in humans.

The claimed invention is directed to administering a lentiviral vector encoding GDNF to a target cell in the brain for treating Parkinson's disease. The specification fully enables the claimed invention. The specification teaches three groups of monkeys. The first group of monkeys included aged monkeys whose brains display specific cellular changes associated with early Parkinson's disease. In the early stage of the disease, the brain cells remain intact but either stop making dopamine, or make less dopamine than normal. The monkeys' brains were analyzed before and after treatment using PET, neuroanatomical, neurochemical and molecular biological techniques. The results showed a significant increase in the production of dopamine, similar to the level of dopamine found in the brains of young monkeys.

The second group of monkeys included young monkeys with no symptoms of Parkinson's disease. To evaluate any changes in function or behavior during the course of the study, each monkey was trained to perform consistently in a hand-reach task that required them to pick-up food treats out of recessed wells. These monkeys were further analyzed on a Parkinsonian clinical rating scale (CRS), an observational assessment of movement analogous to one used by neurologists to assess patients with Parkinson's disease. The CRS analysis and the hand-reach task training indicated that the monkeys did not have any symptoms of Parkinson's disease. The monkeys then received the chemical MPTP, which has been shown to initiate a Parkinson's disease state in monkeys and humans. When the monkeys were tested using the hand-reach and CRS analysis a week later, they could not perform the hand-reach task without difficulty, and the CRS analysis determined the presence of Parkinson's symptoms. The monkeys were then given lenti-GDNF and re-tested a week later. The results revealed that hand-reach improved to levels consistent with performance before the administration of MPTP, and the CRS analysis also showed significant improvement. The monkeys were further subjected to a PET scan, the results of which showed that lenti-GDNF treatment prevented degeneration of the target brain cells and increased dopamine production. Control monkeys in each of the two groups received lenti-βgal, which produced no effect on structure or anatomy of brain cells, and did not improve the impaired behavior of monkeys exhibiting Parkinson's disease.

The third group of monkeys included normal monkeys that received lenti-GDNF and were allowed to survive for eight months. These monkeys showed high levels of GDNF expression, verifying that the lentiviral GDNF delivery system of the claimed invention is capable of long-term expression in target cells of the brain.

It is asserted, on page 7 of the Office Action, that the specification provides no working examples of treatment or prevention of any neurodegenerative disease in humans or any mammal. Applicants disagree; as is discussed in detail above, the specification teaches two different animal models for Parkinson's disease, and shows results that categorically treat Parkinson's disease by the preventing the loss or slowing the degeneration of the dopaminergic cells in the brain.

As stated in MPEP 2164.02, "[a]n *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention." An animal model is acceptable where it is recognized in the art that this model correlates to a specific condition. If this is has not yet been established in the art, the animal model is acceptable if one skilled in the art would accept the model as reasonably correlating to the condition.

This standard (the "reasonableness standard") serves to prevent the PTO from unnecessarily and inappropriately adopting the more stringent standards of the FDA.[1] Moreover, as the Examiner is aware, considerations made by the FDA for approving clinical trials are very different from those made by the PTO in determining whether a claim is enabled, *i.e.*, safety considerations are more properly left with the FDA. *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed Cir. 1994).

In the present invention, the "condition" is Parkinson's disease. The effects of the condition can be reversed by the introduction of a nucleic acid encoding GDNF into the subject, so that the genetic phenotype of the subject is altered. When testing a suitable vector for delivery of the gene product, a good experimental model should test whether 1) the gene product is successfully introduced into a cell and whether 2) the genetic phenotype of the cell is altered as a result. In this case, the cells in question have clearly passed this test, as expression of GDNF and improvement in symptoms of Parkinson's disease are demonstrated in the experimental model.

The following review articles, copies of which are enclosed, provide support that the non-human primate models of the specification are art-recognized and used for correlating to Parkinson's disease in humans. For example, Petzinger *et al.* report, in that last paragraph on

[1] Public hearings were held in San Diego on October 17, 1994, where then PTO Commissioner Bruce Lehman and other PTO representatives received comments on the inappropriate standards that Examiners were applying to biotechnological inventions and as a result of these and other objections raised by the scientific community, the present "reasonableness" standard is now applied.

page 5, that "administration of MPTP into non-human primates results in parkinsonian symptoms including bradykinesia, postural instability, and rigidity." (Animal Models of Movement In: Parkinson's Disease and Movement Disorders, (2002) J. Jankovic, and E. Tolosa, eds., 4th ed., Williams and Wilkens, Baltimore, Md.) Further, Crawley *et al.* report that in "non-human primates, administration of MPTP can induce a stable parkinsonian syndrome that is remarkably similar to the idiopathic disease." (Crawley et al, Current Protocols in Neuroscience (1999) 9.4.1-9.4.32.) In addition, Przedborski *et al.* report that, in humans and non-human primates, "MPTP can produce an irreversible and severe parkinsonian syndrome that replicates almost all of the features of PD, including a tremor, rigidity, slowness of movement, postural instability, and even freezing." (Journal of Neurochemistry, 2001, 76, 1265-1274.) These references provide powerful evidence that the animal model used successfully in the instant application is recognized by one skilled in the art as reasonably correlating to the condition in question, as required by MPEP 2164.02.

The claimed invention is enabled by the specification because the specification teaches results in animal models that can be predictably correlated to the human condition of Parkinson's disease. Furthermore, the specification teaches how to achieve long-term GDNF expression in target cells of the brain and thus, enables the claimed invention.

Page 5 of the Office Action cites Marshall (Science) in support of its assertion that the art is unpredicatable, reporting on the recent decision by the FDA to halt retroviral gene therapy trials in the US based upon the X-linked SCID French trial. It should be noted that the FDA recently announced that it will permit retroviral gene therapy trials citing that, in the context of "the use of retroviruses to insert new genes in blood stem cells" trials would continue on a "case-by-case basis", and further, that "a continuing review of adverse events from **all** US studies involving similar retroviral vectors has so far found no evidence of leukemia believed to be due to the gene therapy" (AAPS Newsmagazine, May 2003; copy enclosed).

The Office Action goes on to cite comments of Kordower *et al.*, relating to the need for further consideration of the lenti-GDNF gene therapy in the clinic. (See page 6 of the Office Action.) To the contrary, Kordower *et al.*, here, are suggesting that in the clinic, it would not be practical to inject into both the striatum and the substantia nigra, so a determination should be made as to the criticality of one injection site over the other. By making the suggestion, it is clear that the researchers do, in fact, believe that the results in the non-human primate models are

correlative to the clinical situation in a human patient, and that only one of the sites should be sufficient to convey the therapeutic effects of GDNF to the patient. To this end, the fact is that Kordower *et al.* and the instant application report successful treatment of Parkinson's disease in an art-recognized non-human primate model of Parkinson's disease. The claims reflect commercially relevant embodiments, and the scope of the claims is commensurate with the teachings of the specification.

Page 7 of the Office Action indicates that the state of the art is "poorly developed (actually nil)." Applicants point out that they are one of the first in the neurological field to demonstrate gene therapy in an art-recognized model for Parkinson's disease using a lentiviral vector. As such, Applicants consider the present invention a pioneer invention in the field of treating Parkinson's disease using gene therapy. A pioneer patent has been defined as one which performs a function never performed by an earlier invention". 239 F.2d 339, 345 (5th Cir. 1986). The Courts have held that, as an incentive to invent and to the prompt, early disclosure of inventions, as well as a reward for having broken new ground, pioneer patents are entitled to broad claims to the broad concept disclosed. In re Hogan, 194 U.S.P.Q. 527, 537 (CCPA, 1977). The Court reasoned in In re Hogan that:

> The PTO has not challenged appellants' assertion that their 1953 application enabled those skilled in the art in 1953 to make and use "a solid polymer" as described in claim 13. Appellants disclosed, as the only then existing way to make such a polymer, a method of making the crystalline form. To now say that appellants should have disclosed in 1953 the amorphous form which on this record did not exist until 1962, would be to impose an impossible burden on inventors and thus on the patent system. There cannot, in an effective patent system, be such a burden placed on the right to broad claims. To restrict appellants to the crystalline form disclosed, under such circumstances, would be a poor way to stimulate invention, and particularly to encourage its early disclosure. To demand such restriction is merely to state a policy against broad protection for pioneer inventions, a policy both shortsighted and unsound from the standpoint of promoting progress in the useful arts, the constitutional purpose of the patent laws.

Id.

Not only can claims to a pioneering invention encompass embodiments that are not specifically disclosed, they can also encompass embodiments not contemplated by the inventor at the time the application is filed. See Phillips Petroleum Co. v. U.S. Steel, 6 U.S.P.Q.2d 1065,

1074 (D.Del. 1987), aff'd 9 U.S.P.Q.2d 1461 (Fed. Cir. 1989) (an inventor may properly claim subject matter than later turns out to be beyond his actual research, so long as his research enables one skilled in the art to make and use the claimed invention as it was understood at the filing date).

While these same principles apply in the present application, it should be appreciated that Applicants are not even trying to claim subject matter that is not specifically disclosed or beyond their actual research, but rather, are claiming subject matter that has been reduced to practice in a correlative animal model, as specified in MPEP 2164.02. Applicants were one of the first to teach, describe and enable the treatment of Parkinson's disease and reversal of its symptoms using a lentiviral-based vector expressing GDNF in a non-human primate model. Using the knowledge in the art and the teachings in the application, the full breadth of the claims are clearly enabled, such that they can be practiced without undue experimentation.

Contrary to the Examiner's conclusion, undue and excessive experimentation is not required on the part of the skilled artisan in order to carry out the invention because, for the reasons detailed above, the specification provides the necessary guidance to enable the claimed invention relating to gene therapy in the treatment of Parkinson's disease.

In view of the amendments and arguments, reconsideration and withdrawal of the Section 112, first paragraph, rejections are requested.

CONCLUSION

In view of the remarks and amendments herewith, it is believed that the application is in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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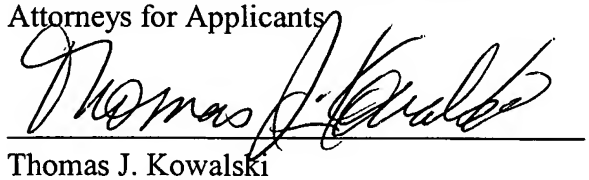
By: 

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